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Preventing hydrolysis

- Formulation of the drug as a powder for reconstitution by water just before use.
  - Refrigeration can keep the product longer after reconstitution.
- Use of buffers.
  - Hydrolysis of most drugs depends on the relative concentrations of the hydroxyl and hydronium ions
  - For most hydrolyzable drugs, optimum stability is on the acid side, somewhere between pH 5 and 6.

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Preventing oxidation

- Oxidation **increases** by:
  1. Increasing temperature.
  2. Keeping the drug in a wet condition.
  3. Exposure to light.
  4. Exposure to some chemicals and trace elements.
- Oxidation usually accompanied by change in color.

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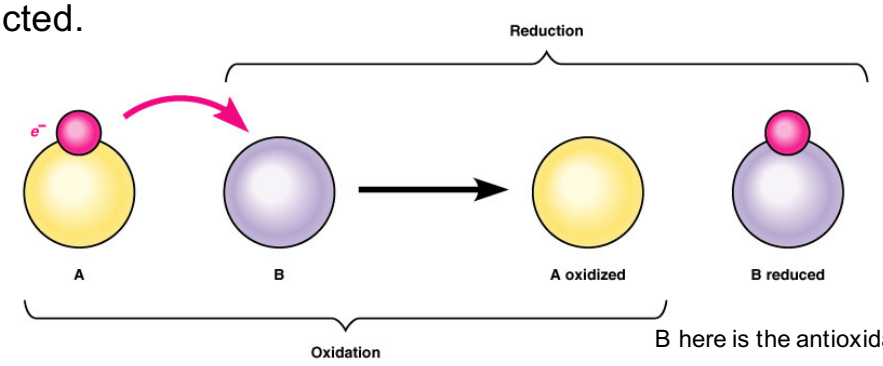
Antioxidants

- Used to prevent oxidation
- Act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected.



B here is the antioxidant

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Antioxidants in pharmacy

In aqueous solutions:

- Sodium sulfite (Na_2SO_3, at high pH values).
- Sodium bisulfite ($NaHSO_3$, at intermediate pH values).
- Sodium metabisulfite ($Na_2S_2O_5$ at low pH values).
- Ascorbic acid.

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Antioxidants in pharmacy

Safety considerations regarding sulfites

- In June 1987, FDA labeling regulations went into effect requiring a warning about possible allergic-type reactions, including anaphylaxis, in the package insert for prescription drugs to whose final dosage form **sulfites** have been added.
- **Sulfites** used in many injectable drugs like antibiotics and local anesthetics; some inhalants and ophthalmic preparations.
- 0.2% of population are hypersensitive to sulfites.
- Asthmatics and other patients who may be sulfite sensitive should be reminded to read the labels of packaged foods and medications to check for the presence of these agents.
- The FDA permits the use of sulfites in prescription products, with the proper labeling, because there are no generally suitable substitutes

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Antioxidants in pharmacy

In oleaginous preparations

- Alpha-tocopherol.
- Butyl hydroxy anisole.
- Other excipients may inactivate the antioxidant
- Antioxidants may react with the drug.

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Preventing oxidation

- Certain pharmaceuticals require an oxygen-free atmosphere during preparation and storage.
- Oxygen-sensitive drugs may be prepared in the dry state and packaged in sealed containers with the air replaced by an inert gas such as nitrogen, as may liquid preparations.

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Trace elements and oxidation

- They can originate from container, stopper, solvent, etc.
- They can accelerate the oxidative process

Example

- The rate of formation of color in epinephrine solutions is greatly increased by the presence of ferric, ferrous, cupric, and chromic ions.

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Trace elements and oxidation

- Great care must be taken to eliminate trace metals from labile preparations by:
  - Thorough purification of the source of the contaminant
  - Chemically complexing or binding the metal through the use of specialized agents

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Light and oxidation

- Light increases the energy of drug molecules making them more reactive.
  - Energy increased due to exposure to photons
  - Possibility of oxidation increases
  - Drugs protected from light by using opaque containers
- USP. Potassium iodide in solution is prone to photocatalyzed oxidation and the release of free iodine, with a resultant yellow-to-brown discoloration of the solution.
  - Light resistant containers
  - 0.5 mg of sodium thiosulfate for each gram of potassium iodide.
  - Sodium thiosulfate converts it to colorless and soluble sodium iodide

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Temperature and pH

➢ Temperature

- Increasing temp accelerates degradation.
  - Keep oxidizable drugs in cold place.

➢ pH

- Each drug must be maintained in solution at the pH most favorable to its stability.

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Oxidation - summary

- The formulation pharmacist may stabilize the preparation by:
  - The selective exclusion of oxygen, oxidizing agents, trace metals, light, heat, and other chemical catalysts to the oxidation process.
  - Antioxidants, chelating agents, and buffering agents may be added to create and maintain a favorable pH.

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Other destructive processes

- Polymerization
- Decarboxylation
- Deamination
  - Less frequent than hydrolysis and oxidation

Some USP Drugs And Preparations Especially Subject To Chemical Or Physical Deterioration

PREPARATION	CATEGORY	MONOGRAPH OR LABEL WARNING
Epinephrine bitartrate ophthalmic solution	Adrenergic	Do not use inhalation, injection, nasal, or ophthalmic solution if it is brown or contains a precipitate
Epinephrine inhalation solution Epinephrine injection Epinephrine nasal solution Epinephrine ophthalmic solution		
Isoproterenol sulfate inhalation, solution	Adrenergic (bronchodilator)	Do not use inhalation or injection if it is pink to brown or contains a precipitate
Isoproterenol inhalation solution		
Nitroglycerin tablets	Antianginal	To prevent loss of potency, keep in original container or supplemental container specifically labeled suitable for nitroglycerin tablets
Paraldehyde	Hypnotic	Subject to oxidation to form acetic acid